REMARKS

Claim 1 has been amended to replace "mechanically" with "microsurgically." Support for this amendment is found on page 2, in paragraph 6, of the specification. It is believed that this clarifies the meaning of "mechanically." Previously, the Office objected to the phrase "microsurgically" removing cells "from a location in the tissue" based on this latter phrase. However, this phrase no longer appears in the claims and no attempt has been made to reinstate it.

It is understood that microsurgical techniques are those applied to intact natural tissue and thus the meaning of the claim is further clarified.

Although this amendment is made after final rejection, entry is requested, because it is believed that this amendment places all claims in a position for allowance for the reasons that follow.

The invention permits, for the first time, living cells to be isolated directly from a tissue so that the surroundings of the cells are known when further experimentation is done. None of the cited art suggests or enables such a procedure. While it may sound straightforward to label a cell through the expression of a fluorescent protein and then microsurgically remove it by observing the fluorescence in the cells removed, there is no suggestion in the art that this be done. The fact that the invention may seem to make sense after it has already been invented is not a fair basis for rejection.

Applicants respond specifically to the outstanding rejections as follows:

All claims 1-2 and 5-12 were rejected as obvious over Hadjantonakis, *et al,*(*Histochem. Cell Biol.* (2001) 115:49-58) in view of Trumper, *et al.* (*Blood* (1983) 81:3097-3115). Rashidi

(*Clin. Exp. Metastasis* (2000) 18:57-60) is mentioned in the statement of this rejection, but not further discussed.

The interpretation placed by the Examiner on Hadjantonakis is entirely correct. Hadjantonakis digests the tissue, thus obliterating the surroundings of the cell that is to be removed, and further isolates the cell by flow cytometry. This is not a microsurgical technique.

This deficiency is not remedied by Trumper who also uses cell suspensions obtained from tissues as a source of the cells to be examined. (See page 3098, left-hand column, "Preparation of HD Lymph Nodes.") Figure 1 clearly shows that the cells have been suspended, and are not microsurgically removed from intact tissue containing the surrounding cells. Accordingly, the composition of Hadjantonakis and Trumper actually teach away from the invention as claimed. Therefore, this basis for rejection may properly be withdrawn.

Claims 1, 6, 7, 10 and 12 were rejected as anticipated by Schindler (*Nature Biotechnology* (1998) 16:719-720).

Respectfully, Schindler does not describe a "microsurgical" technique. Rather, as the Office recounts, any tissue explants are placed on a thermoplastic film and portions excised by cutting through the film, not the tissue as would be the case in microsurgical techniques. This is not a technique that can be performed in living animals as is claimed in claim 12. Support for claim 12 is found in paragraph 26 of the application. Applicants note that there is no written description rejection of claim 12.

For these reasons, this rejection may be withdrawn.

All claims were rejected as assertedly obvious over the combination of Hadjantonakis in view of Rashidi and Schindler. Again, applicants see no further mention of Rashidi in the description of the rejection.

It is unclear how the combination of Hadjantonakis and Schindler would result in or suggest the invention. Neither document teaches microsurgical techniques for removal of cells from the surrounding cells in a tissue. Hadjantonakis teaches enzyme digestion and Schindler teaches a laser technique on isolated film-bound explants which does not address the tissue in a native form for evaluation. Rather, the tissue is completely artificially maintained attached to a thermoplastic film. Microsurgery requires use of an intact and nature tissue.

All claims were rejected as assertedly obvious over the combination of Hadjantonakis in view of Rashidi and BioRad Microscience's press release of 15 October 2001. Once again, Rashidi is not mentioned in the context of the rejection.

Applicants have difficulty discerning any major difference between the BioRad description and Schindler. As was the case with regard to the combination of Hadjantonakis and Schindler, neither document suggests microsurgical techniques for removal of individual cells from living tissue. In both cases, the tissue is placed into an unnatural situation not typical of its native environment by adherence to a thermoplastic film. Hadjantonakis, of course, teaches away from microsurgical techniques entirely. Therefore, the combination cannot very well suggest microsurgery.

The issue of rejections based on a combination of documents is not germane; the argument is not that the combination would not suggest the employment of green fluorescent protein or

other fluorescent proteins in the BioRad technique, but rather that neither document teaches microsurgical removal of an individual cell from a living tissue.

Conclusion

The claims have been amended to emphasize that the techniques used are microsurgical techniques which is clearly supported in the specification as set forth above. "Microsurgical" clearly denotes that the techniques are directed to manipulating tissue that is in its native state. For example, one definition of surgery is:

> Operative procedures on organs, regions or tissues in the treatment of diseases, including tissue section by lasers, also organs, tissues or cells for transplantation from one site to another within the same subject or from one subject to another in the same species or different species

or

> Operation to remove or repair a part of the body or to determine if disease is present.

While laser techniques are included, the type of laser dissection described by Schindler (ACAS) and BioRad does not meet the definition of microsurgical because the tissue is splayed against a thermoplastic film, and it is not the tissue that is addressed by the laser beam, but rather a film to which the tissue is artificially bound. The techniques claimed in the present claims have the decided advantage of elucidating the position of the excised cell in the natural tissue sample.

In all of the foregoing rejections, it is assumed that Rashidi is added only because tumor cells are used in that document. Applicants, however, assert that their technique is patentable regardless of its application to tumor or other tissues.

Therefore, applicants respectfully request that the amendment to claim 1 be entered and that claims 1-2 and 5-12 be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762004100.

Respectfully submitted,

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